146. The host cell of claim 145, wherein said nucleic acid is operably associated with a heterologous regulatory sequence.

147. A method of producing a polypeptide comprising culturing the host cell of claim 146 under conditions such that a polypeptide is expressed, and recovering said polypeptide.

148. A composition comprising the isolated polynucleotide of claim 137.--

Remarks

Upon entry of the foregoing amendment, claims 24-100 and 105-148 will be pending in the application, with claims 24, 51, 75, 84, 105, 107, 109, 111, 121, 128 and 137 being the independent claims. Claims 11-16, 19 and 101-104 have been canceled. Claims 46, 48, 70, 72, 75, 79, 81, 84, 105-108, 116, 118, 121, 125, 127-128, 132, and 134 have been amended taking the Examiner's comments into consideration. This amendment introduces no new matter and entry thereof is respectfully requested.

Support for the amended and new claims can be found throughout the application. In particular, support for claims 46, 48, 70, 72, 79, 81, 116, 118, 125, 127, 132 and 134 can be found, *inter alia*, at page 27, line 16, to page 28, line 4. Support for claim 75 can be found, *inter alia*, at page 9, lines 1-5; at page 36, lines 25-28; and at page 50, lines 22-25. Support for claim 84 can be found, *inter alia*, at page 25, lines 10-16. Support for claims 105-108 can be found, *inter alia*, at page 18, line 30, to page 19, line 1. Support for claim 121 can be found, *inter alia*, at page 5, lines 20-27; and at page 18, lines 9-11. Support for claim 128 can be found, *inter alia*,

at page 23, lines 9-13. Support for new claims 137-148 can be found, *inter alia*, at page 25, lines 10-16. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Submission of Substitute Sequence Listing

Applicants submit herewith a substitute sequence listing. In particular, Applicants have amended the sequence listing to indicate that SEQ ID NO:3 is a protein sequence from *Drosophila melanogaster* and not *Homo sapiens*, and to add a Thr residue, which was inadvertently omitted, as the first residue of the sequence in SEQ ID NO:3. Support for these amendments can be found in the specification, *inter alia*, at page 2, line 28, to page 3, line 2, and in document AS14 recited on PTO Form-1449 submitted on June 4, 1999. Applicants have further provided the correct first name and initial of inventor Kunsch, which is Charles A. instead of Chuck. Support for this amendment can be found in the Declaration submitted on January 11, 1999.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objections to the Drawings

The Examiner has indicated that the drawings are objected to "because Table 1 . . . has not been referred to as a separate drawing in the 'Brief Description of the Drawings.' It is unclear whether applicants intend Table 1 to be a drawing or part of the specification." (Paper No. 11

at page 3.) The Examiner further indicated that if Table 1 is part of the specification, it should be inserted into the specification and the specification pages renumbered accordingly. *Id.*

Applicants submit that they intended Table 1 to be part of the specification. Therefore, the Examiner is respectfully requested to renumber Table 1 as pages 103-107 and insert it at the end of the specification, and to renumber the remaining pages of the specification.

Claim objections

The Examiner indicated that claims 128-136 are objected to because claim 128 allegedly is poorly written and does not clearly reflect the description of the embodiment as disclosed on pages 19-23 of the specification. (Paper No. 11 at page 3.) The Examiner suggested amending the claim to remedy the alleged ambiguities.

Consistent with the Examiner's suggestion, Applicants have amended claim 128. Accordingly, withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 75-83 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. (Paper No. 11 at page 4.) According to the Examiner, "[t]he specification as originally filed provides no clear support for fragments that regulate generic 'epithelial gene expression'." *Id.*

Applicants submit that the specification, for example, at page 9, lines 1-5, indicates that because Ets-4 is thought to be important as a transcription factor in *Drosophila melanogaster*

germline development, the homology between Ets-4 and PDEF suggests that PDEF may also regulate epithelial specific gene expression. Furthermore, the specification, at page 36, lines 25-28, indicates that PDEF is primarily expressed in the epithelial cells of the prostate. Applicants have amended claim 75 to recite a fragment of SEQ ID NO:2, wherein said fragment regulates "prostate-specific" epithelial gene expression. One of ordinary skill in the art reading the specification will understand that PDEF and fragments thereof can function as transcription factors, like the *Drosophila* homolog Ets-4, to regulate the expression of prostate-specific epithelial genes, such as the prostate-specific antigen (PSA). Thus, the specification as filed clearly provides support for fragments of PDEF that regulate prostate-specific epithelial gene expression. Therefore, one skilled in the art would readily recognize that Applicants were in possession of the fragments specified in the claims. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1118-19 (Fed. Cir. 1991); and *Union Oil Co. of California v. Atlantic Richfield Co.*, 99-1066, 2000 U.S. App. LEXIS 5477 (Fed. Cir. March 29, 2000, decided). Accordingly, withdrawal of this rejection is respectfully requested.

Claims 24, 38-51, 64-83 and 121-127 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. (Paper No. 11 at page 5.) The Examiner stated that deposit of the clone under the terms of the Budapest Treaty and a Declaration assuring that all restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent would satisfy the deposit requirements. *Id.*

Applicants submit herewith a Declaration for Deposited Biological Materials, which complies with these requirements. Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner further rejected claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111 and 113-120 under 35 U.S.C. § 112, first paragraph, because allegedly "the specification, while being enabling for a 'nucleic acid' that encodes SEQ ID NO:2 or a fragment of SEQ ID NO:2 (as recited in the claims), does not reasonably provide enablement for polynucleotides that do not encode SEQ ID NO:2 or a recited fragment of SEQ ID NO:2." (Paper No. 11 at page 6.) Applicants respectfully traverse this rejection.

The Examiner contended that "[a]ll of the utilities for polynucleotides taught in the specification require that either the polynucleotide will hybridize with a PDEF nucleic acid or that it encode a polypeptide, either with PDEF function or that can be used to make antibodies that will be specific for a PDEF protein." (Paper No. 11 at page 6.)

Contrary to the Examiner's position, the specification teaches numerous additional utilities for the claimed polynucleotides. For example, the specification, at pages 29-33 and 46, teaches that polynucleotides can be used as primers or probes for *in situ* hybridization; in Northern blot analysis; to control gene expression through triple helix formation or antisense DNA or RNA; for gene therapy; for identifying individuals through restriction fragment length polymorphism (RFLP) analysis; to identify DNA sequences which are targets for PDEF; and to identify novel target genes by cDNA array transcriptional profiling. A single utility is all that is required to satisfy 35 U.S.C. § 112. *See Raytheon Co. v. Roper Corp.*, 220 USPQ 592 (1983).

The Examiner also contended that "[r]elative to a specific polynucleotide, e.g. the open reading frame of SEQ ID NO:1, the vast majority of polynucleotides that encode the same amino acid sequence would be closer to 65% identical than to 100% identical . . . ." and "the vast

majority could not be used in hybridization against any target disclosed in the specification, i.e., SEQ ID NO:1." (Paper No. 11 at pages 6-7.)

Applicants submit that the claims do not recite polynucleotides that are 65% identical to SEQ ID NO:1. The claims recite polynucleotides that are at least 90% identical to nucleic acids encoding a PDEF protein (SEQ ID NO:2). Such polynucleotides, as discussed *supra*, in addition to being useful for hybridization, are also useful, *inter alia*, as primers or for raising antibodies.

The Examiner further contended that "[i]t is not clear that an antibody that recognizes a peptide sequence differing in 10% or more of amino acids would bind to a PDEF polypeptide or peptide fragment . . . ." and "[i]t is unclear how one skilled in the art could predict which of all the possible variant amino acid sequences could be used to make a suitable antibody to the PDEF protein, and the specification provides no guidance on the matter." (Paper No. 11 at page 8.) The Examiner also contended that "[t]he specification does not provide any guidance on what amino acid residues are necessary and sufficient for PDEF biological activity." *Id.*

Contrary to the Examiner's position, the claims do not require that the polynucleotide encode a biologically active protein. The specification teaches, at page 25, which amino acid residues comprise epitope-bearing portions of the PDEF protein. One of ordinary skill in the art would know which amino acid residues encoded by the polynucleotide of the claims could be substituted and still constitute a polypeptide which is capable of raising antibodies to the PDEF protein, and could routinely make and use the polypeptides to raise antibodies. Applicants need not disclose every species encompassed by a claim to satisfy the requirements of 35 U.S.C. § 112. *In re Angstadt*, 190 USPQ 214, 218 (C.C.P.A. 1976).

In addition, claim 105 as amended, recites an isolated polynucleotide comprising a nucleic acid at least 95% identical to a nucleic acid encoding 60 contiguous amino acids of SEQ

ID NO:2. As discussed *supra*, the specification teaches which amino acid residues comprise epitope-bearing portions of the PDEF protein. One of ordinary skill in the art would know which fragments of 60 or more contiguous amino acids of SEQ ID NO:2 include one or more of these epitope-bearing regions. These fragments, which include one or more epitope-bearing regions, are useful for producing polypeptides that are capable of raising antibodies. One of ordinary skill in the art would know which amino acid residues not to substitute or delete in fragments of SEQ ID NO:2 to produce a polypeptide that is useful for raising antibodies to the PDEF protein, and could routinely make and use the polypeptides to raise antibodies. Thus, one of ordinary skill in the art would know which fragments of SEQ ID NO:2 are useful for producing polypeptides that are capable of raising antibodies.

The specification clearly teaches one of ordinary skill in the art how to use polynucleotides that are 90% or 95% identical to a reference nucleic acid encoding a PDEF protein or fragment. Thus, Applicants have provided sufficient guidance to one of ordinary skill in the art to determine which polynucleotides encompassed by the claims would be useful for making a polypeptide capable of raising antibodies without "excessive trial and error experimentation." Accordingly, withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 43, 46, 48, 67, 70, 72, 73, 76, 79, 81, 82, 113, 116, 118, 119, 125, 127, 129, 132, 134 and 135 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. (Paper No. 11 at page 11.)

According to the Examiner, claims 43, 67, 76, 113, 122 and 129 are indefinite for recitation of "heterologous polynucleotide" because the claims do not clearly indicate which nucleic acids are "heterologous" or in which context they are "heterologous." *Id.*

Applicants note that the term "heterologous" is used in the captioned application to describe the generation of fusion proteins. (*See* specification, at page 25, line 28, to page 26, line 13; and at page 60, lines 18-21.) In regard to fusion proteins, the specification states as follows:

> Any PDEF polypeptide can be used to generate fusion proteins. For example, the PDEF polypeptide, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the PDEF polypeptide can be used to indirectly detect the second protein by binding to the PDEF. Moreover, because secreted proteins target cellular locations based on trafficking signals, the PDEF polypeptide can be used as a targeting molecule once fused to other proteins.
>
> Examples of domains that can be fused to PDEF polypeptides include not only heterologous signal sequences, but also other heterologous functional regions.

(Specification, at page 25, line 28, to page 26, line 5.)

In view of the above disclosure, one skilled in the art reviewing the specification would clearly understand that the phrase "heterologous polynucleotide," as it is used in the context of claims 43, 67, 76, 113, 122 and 129, refers to a polynucleotide that is not normally associated with the PDEF polynucleotide. Accordingly, withdrawal of this rejection is respectfully requested.

Regarding claims 46, 48, 49, 70, 72, 73, 81, 82, 116, 118, 119, 125, 127, 132, 134 and 135, the Examiner stated that the claims are indefinite for recitation of "heterologous regulatory sequence" because "the claim does not provide the context of 'regulatory'; there is no indication of what is regulated, transcription, translation, replication, enzyme activity, etc. Also, there is

no clear indication as to what the 'heterologous regulatory sequence' is 'operably associated'." (Paper No. 11 at pages 11-12.) The Examiner suggested amending the claims to remedy the alleged ambiguities.

Solely in an effort to advance prosecution, Applicants have amended claims 46, 48, 70, 72, 79, 81, 116, 118, 125, 127, 132 and 134 to recite that the first nucleic acid is operably associated with a heterologous regulatory sequence. Furthermore, Applicants point out that one of ordinary skill in the art knows that a regulatory sequence can mean, for example, a promoter sequence, a binding site within the promoter sequence, an operator, an enhancer, or other regulatory sequence involved in gene expression (e.g., transcription). Accordingly, withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 84, 101-108, 113-118 and 120-136 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by GenBank Accession No. AA662204. (Paper No. 11 at pages 12-13.) According to the Examiner, GenBank Accession No. AA662204 comprises a nucleic acid 514 nucleotides in length, which encodes amino acids 277-335 of SEQ ID NO:2. *Id.*

Applicants have canceled claims 101-104 and have amended claims 84, 105-108, 121 and 128. Thus, this rejection has been rendered moot.

Regarding claim 128, the Examiner also noted that "claim 128, as written, embraces any polynucleotide comprising a nucleic acid that encodes an amino acid sequence comprising at least one codon for an amino acid from positions 15-321 of SEQ ID NO:2. For example, if m and n both equal the same integer between 15 and 321." *Id.*

Applicants note that claim 128, as amended, recites that m is less than n. Thus, m and n

do not equal the same integer between 15 and 321.

The Examiner further rejected claims 84, 103 and 128-136 under 35 U.S.C. § 102(b) as allegedly being anticipated by Chen *et al.*, *Dev. Biol. 151*:176-191 (1992). (Paper No. 11 at pages 12-13.) According to the Examiner, amino acids 71-94 of the *Drosophila* ets-4 polypeptide are identical to amino acids 294-317 of SEQ ID NO:2. *Id.*

As indicated *supra*, Applicants have canceled claim 103 and amended claims 84 and 128. Thus, this rejection has been rendered moot.

Double patenting

The Examiner stated that should claims 27, 30, 33 and 36 be found allowable, claims 54, 57, 60 and 63 would be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. (Paper No. 11 at page 14.)

In response, Applicants note that they are entitled to claim the invention using multiple claims, so long as the claim set as a whole clearly defines the subject matter of the invention. *See* M.P.E.P. § 2173.05(n). Further, Applicants note that claims 27, 30, 33 and 36 and 54, 57, 60 and 63 are not duplicative, because claims 27, 30, 33 and 36 are drawn to an isolated polynucleotide comprising a *nucleic acid* at least 90% identical to a reference nucleic acid encoding certain amino acids of SEQ ID NO:2, whereas claims 54, 57, 60 and 63 are drawn to an isolated polynucleotide comprising a nucleic acid encoding an *amino acid sequence* at least 90% identical to a reference amino acid sequence encoding certain amino acids of SEQ ID NO:2. Accordingly, withdrawal of this objection is respectfully requested.

Allowable Subject Matter

The indication that claims 27, 30, 33, 36, 54, 57, 60, 63, 85-100, 110 and 112 are allowable if rewritten in independent form is noted and appreciated by Applicants.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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